

L103,982



PATENT SPECIFICATION

NO DRAWINGS

L103,982

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No. 36700/67.

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(Divided out of No. 1,103,574).

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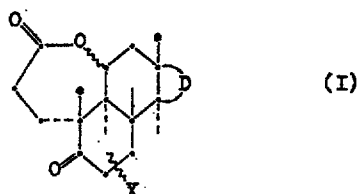
COMPLETE SPECIFICATION

Novel 3,5-Seco-A-Nor-Steroid Derivatives

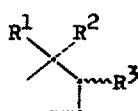
We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

5 The present invention is concerned with novel 3,5-seco-A-nor-steroid derivatives. 5

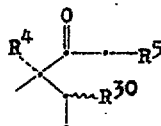
The novel 3,5-seco-A-nor-steroid derivatives provided by the invention are compounds of the general formula



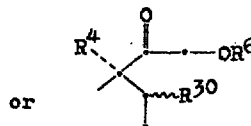
10 wherein X represents a hydrogen or halogen atom or a lower-alkyl, lower-alkylthio or lower-alkanoylthio group in the 6- or 7-position and D represents a grouping of the formula 10



(Ia)



(Ib)



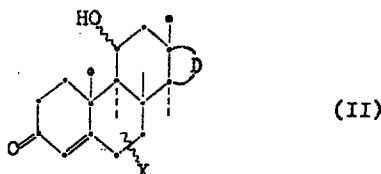
(Ic)

15 in which R¹ represents a hydroxy or esterified hydroxy group, R² represents a hydrogen atom or a lower-alkyl group or R¹ together with R² represents an oxo, lower-alkylenedioxy or 17β-hydroxy-17α-(lower alkanolic acid) lactone group, R³ represents a hydrogen atom or a lower-alkyl, hydroxy or esterified hydroxy group, R⁴ represents a hydrogen or halogen atom or a lower-alkyl, hydroxy or esterified hydroxy group, R⁵ represents a hydrogen or halogen atom, OR⁶ represents a hydroxy or esterified hydroxy group and R³⁰ represents a hydrogen or fluorine atom or a lower-alkyl, hydroxy or esterified hydroxy group, and alkali-metal salts of the corresponding keto-acids. 20

The novel steroid derivatives provided by the invention are of value as intermediates in the manufacture of 9β,10α-steroids of the androstane and pregnane series,

for example, via the desA-steroids which form the subject matter of our copending application for Letters Patent no. 36703/67 (now serial no: 1,103,985).

The novel compounds of formula I hereinbefore can be prepared by subjecting an 11-hydroxy-androst(or pregn)-4-en-3-one of the general formula

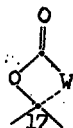


(wherein X and D have the significance given earlier) to an oxidative ring-opening of the A-ring by ozonolysis or treatment with hydrogen peroxide.

The oxidative ring-opening of the A-ring of the 11-hydroxy-androst(or pregn)-4-en-3-one of formula II is preferably effected by ozonolysis. The ozonolysis is suitably carried out in an organic solvent; for example, acetic acid, ethyl acetate, methanol, chloroform or methylene chloride or a mixture of two or more of such solvents such as (ethyl acetate)/(acetic acid) or (ethyl acetate)/(methylene chloride). Moreover, the ozonolysis is advantageously conducted at below room temperature. Thus, it is preferably conducted at a temperature between about -70°C and 25°C . The resulting ozonides can be decomposed by conventional means; for example, by treatment with water, hydrogen peroxide in water, acetic acid or ethyl acetate. The oxidative ring-opening of the A-ring of an 11-hydroxy-androst(or pregn)-4-en-3-one of formula II can also be effected by treatment with hydrogen peroxide.

The compounds of formula I obtained according to the foregoing oxidative ring-opening can be treated with an alkali-metal hydroxide such as sodium hydroxide to give the salt of the corresponding keto-acid.

It will be appreciated that the term 'lower alkyl' is used in this description and in the accompanying claims to mean both straight-chain and branched-chain alkyl groups containing not more than six carbon atoms (e.g. methyl, ethyl, propyl and isopropyl). The term 'lower alkanoyl' means an alkanoyl group containing not more than six carbon atoms (e.g. acetyl). The term 'halogen' means iodine, bromine, chlorine and fluorine. The expression '17 β -hydroxy-17 α -(lower alkanoyl) lactone' refers to a configuration at the C-17 carbon atom as illustrated as follows:



wherein W is a lower-alkylene group such as ethylene or propylene. The term 'lower alkylene' denotes an alkylene group containing not more than six carbon atoms. With regard to X, the preferred derivatives provided by the invention are those in which it represents a hydrogen atom or a lower-alkyl group in the 6- or 7-position or a halogen atom in the 7-position.

The esterified hydroxy groups referred to earlier can be derived from any available acid which will form an ester that can subsequently be hydrolysed to regenerate the hydroxy group. Examples of acids which are suitable for this purpose are alkanoyl acids containing not more than six carbon atoms (e.g. acetic acid), caproic acid, benzoic acid, phosphoric acid and alkane dicarboxylic acids containing not more than six carbon atoms (e.g. succinic acid).

The following Example illustrates the manner in which the novel 3,5-seco-A-nor-steroid derivatives provided by the invention may be prepared:

EXAMPLE

A solution of 6.4 g of 11 α -hydroxy-progesterone in 100 ml of ethyl acetate and 50 ml of methylene chloride was treated with ozone at -70°C until the solution became blue in colour. Oxygen was then passed through and the solution evaporated *in vacuo* at room temperature. The so-obtained syrupy residue was dissolved in 100 ml

of glacial acetic acid and, after the addition of 5 ml of 30 per cent hydrogen peroxide, left for 24 hours at 2°C (in an ice-box). The solution was then evaporated *in vacuo* and the residue triturated with ether, yielding crystals. Recrystallization from acetone yielded 11 α -hydroxy-3,5-seco-A-norpregnane-5,20-dione-3-oic acid 3,11-lactone of melting point 253°—256°C. $[\alpha]_D^{25} = +193.3^\circ$ (c=1 in chloroform).

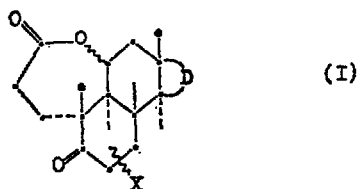
A methanolic solution of 7.5 g of 11 α -hydroxy-3,5-seco-A-norpregnane-5,20-dione-3-oic acid 3,11-lactone was treated with one equivalent of 10-N sodium hydroxide solution and then evaporated to dryness to yield the sodium salt of the corresponding keto-acid.

It will be appreciated that when compounds of the pregnane series are referred to in this specification these compounds are of the 17 β -pregnane series unless specifically indicated to the contrary.

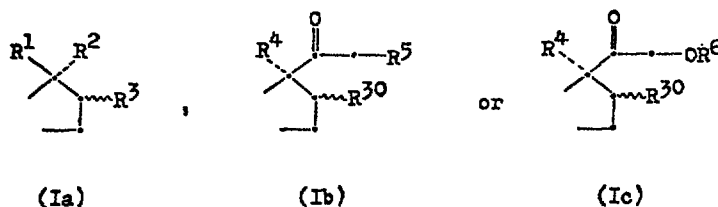
It will be appreciated that in the formulae given in this description and accompanying claims the dots denote carbon atoms or CH, CH₂ or CH₃ groups, the residual valencies being satisfied by hydrogen atoms; such valencies only being shown to indicate hydrogen atoms when configuration is of significance, and then as untruncated solid or broken lines. Valencies shown as solid lines denote β -configuration and those shown as broken lines denote α -configuration. The dots representing angular methyl groups are enlarged solely for reasons of clarity.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



wherein X represents a hydrogen or halogen atom or a lower-alkyl, lower-alkylthio or lower-alkanoylthio group in the 6- or 7-position and D represents a grouping of the formula



in which R¹ represents a hydroxy or esterified hydroxy group, R² represents a hydrogen atom or a lower-alkyl group or R¹ together with R² represents an oxo, lower-alkylene-dioxy or 17 β -hydroxy-17 α -(lower alkanolic acid) lactone group, R³ represents a hydrogen atom or a lower-alkyl, hydroxy or esterified hydroxy group, R⁴ represents a hydrogen or halogen atom or a lower-alkyl, hydroxy or esterified hydroxy group, R⁵ represents a hydrogen or halogen atom, OR⁶ represents a hydroxy or esterified hydroxy group and R³⁰ represents a hydrogen or fluorine atom or a lower-alkyl, hydroxy or esterified hydroxy group, and alkali-metal salts of the corresponding keto-acids.

2. 5-20-Dioxo-11 α -hydroxy-3,5-seco-A-norpregnan-3-oic acid 3,11-lactone.

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of glacial acetic acid and, after the addition of 5 ml of 30 per cent hydrogen peroxide, left for 24 hours at 2°C (in an ice-box). The solution was then evaporated *in vacuo* and the residue triturated with ether, yielding crystals. Recrystallization from acetone yielded 11 α -hydroxy-3,5-seco-A-norpregnane-5,20-dione-3-oic acid 3,11-lactone of melting point 253°—256°C. $[\alpha]_D^{25} = +193.3^\circ$ (c=1 in chloroform).

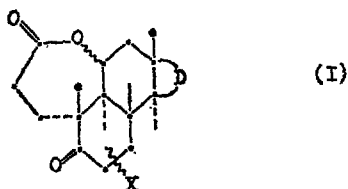
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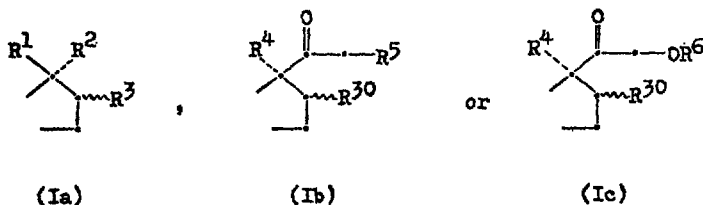
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